

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Interventions addressing the adolescent HIV continuum of care in South Africa: a systematic review and modified Delphi analysis
AUTHORS	Zanoni, Brian; Archary, Moherndran; Sibaya, Thobekile; Ramos, Tatiana; Donenberg, Geri; Shahmanesh, Maryam; Celum, Connie; Pettifor, Audrey; Bekker, Linda Gail; Haberer, Jessica

VERSION 1 – REVIEW

REVIEWER	Lyon, Maureen George Washington University School of Medicine and Health Sciences, Pediatrics
REVIEW RETURNED	04-Dec-2021

GENERAL COMMENTS	<p>This manuscript is a systematic review and Delphi analysis of intervention studies conducted in South Africa with adolescents (ages 10-24), entitled "Interventions addressing the adolescent HIV continuum of care in South Africa: a systematic review and Delphi analysis" (MS # bmjopen-2021-057797).</p> <p>This is a very important study which used scientifically rigorous methods to conduct a review of the literature on interventions addressing the HIV continuum. Given HIV/AIDS is the leading cause of death for adolescents in South Africa, the importance of this article for improving the continuum of care for HIV positive adolescents cannot be overstated. The results from this review have the potential for a very high impact on linkages with care of newly diagnosed HIV positive persons, as well as promising approaches that may help transition adolescents to adult health care facilities based on what has worked with engagement in care interventions.</p> <p>The title appropriately reflects the content of the manuscript.</p> <p>The abstract is a good summary of the findings and includes all essential elements.</p> <p>Introduction. The introduction notes the gaps in knowledge particularly with respect to linking newly diagnosed adolescents with care and transitioning HIV positive adolescents to adult health care facilities. The introduction sets up the purpose of the study highlighting what is known. Particularly striking is that only 10% of adolescents living with HIV are virally suppressed, despite one of the largest antiretroviral therapy programs in the world.</p> <p>Methods.</p>
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	<p>Use of the PRISMA guidelines is a strength of this study. The Delphi analysis with experts from the National Institutes of Health's Fogarty International Adolescent HIV Implementation Science Alliance—South Africa further strengthens the analysis of the findings of this review. A response rate of 50% or more in a survey is considered excellent. The investigators had a response rate of 69% to the REDCap survey to evaluate the identified studies meeting the inclusion criteria, further strengthening the validity and reliability of the study findings.</p> <p>Data analysis. Appropriate methods were used for ranking the eligible articles using the PRISMA 2020 Checklist methods, including the experts in the Delphi analysis.</p> <p>Findings. The findings are clearly presented in the tables and reflected in the text of the manuscript.</p> <p>The descriptive Tables 1-3 are very clear.</p> <p>Discussion and conclusion follow from the systematic review. The identify important elements of effective interventions for adolescents that can guide future research into linkages to care and transition to adult health care, as well as what interventions work best, specifically in-home and HIV-self testing, community-based adherence support, and provision of adolescent-friendly services. The authors suggest future research should assess the cost of interventions but given limited resources perhaps the priority should be finding what works most effectively to link adolescents with care, adhere to ART treatment, and to help them transition to adult health care, irrespective of the relative costs, given this is the leading cause of death in South Africa for this age group.</p> <p>To summarize, identified scalable interventions that could improve the adolescent HIV continuum of care in South Africa that can be acted upon immediately. Investigators also identified gaps in the identification of evidence-based interventions that could effectively link adolescents living with HIV to care and to help the transition to adult health care services.</p> <p>Investigators report the limitations of their findings in detail and the list is comprehensive.</p> <p>I had a few minor suggestions to improve the manuscript:</p> <p>Page 7 Line 18 "...and scale..." Please consider using the word "scalability" here to parallel the use of the word "feasibility" in the previous phrase.</p> <p>Page 9 Line 14 "...nine discussed costing of the intervention." The use of the word "costing" here is awkward. Please consider rewriting.</p> <p>Page 15 Lines 17-20. Although there was no statistically significant difference in community-based support in one study with respect to viral failure after 3-5 years, that 8.8% in the intervention group had viral failure compared to 37.2% in the standard of care group is clinically meaningful and this should be noted. The authors might also want to comment on why this was not statistically significant, e.g. were there so many cases lost to</p>
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	follow up that the sample was too small to find a statistical difference?
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REVIEWER	Casale, Maj University of Oxford Department of Social Policy and Intervention
REVIEW RETURNED	19-Jan-2022

GENERAL COMMENTS	<p>This is an overall well-written and well-structured paper on an important topic, given the persistent high loss to follow up across the continuum of care among adolescents and limited evidence of effective interventions – as highlighted by the authors. I also found the combination of a systematic review and Delphi survey original and interesting. I have mainly minor comments for consideration by the authors:</p> <p>Objective:</p> <ul style="list-style-type: none"> - pg 4: I'm not sure one can refer to expanding implementation of interventions as an objective of the study reported in this paper. Perhaps something along the lines of the identification of promising interventions to be scaled up? <p>Methods</p> <ul style="list-style-type: none"> - Pgs 4/5: It would be useful to be clearer upfront about the inclusion (versus simply exclusion) criteria for the systematic review, e.g. that the review could include intervention studies aimed at increasing or promoting one of more of the following: testing, linkage to care, retention etc - It would be useful to include further information on the search strategy in supplementary material, including an example search string used. It would also be useful to indicate which data were extracted from the papers and presented to Delphi survey participants - Similarly, it would be useful to specify in the paper which tool or template was used for assessment of bias/strength of evidence. Perhaps the grading or scoring table could also be included among supplementary material? - Was there any basis for the cutoff scores used for inclusion of interventions in the second round questionnaire (e.g. impact score above 70)? <p>Discussion</p> <ul style="list-style-type: none"> - Besides making the case for the potential scale up of specific types of interventions that appear to be both effective and feasible, I wondered whether the authors could extend these arguments to consider the potential for combination or integrated interventions. Do the authors have any thoughts, based on these findings, on the potential to roll out or scale up some of these interventions in combination and how best to do this? - Another important point to consider, beyond intervention effectiveness and feasibility, is what adolescents are likely to find acceptable. Work I was recently involved in highlighted concerns around stigma and confidentiality, for example, among potential barriers to adolescent acceptability of interventions (https://bmjopen.bmj.com/content/11/12/e055160). The authors allude to acceptability briefly in relation to self-testing on page 15 but it is an issue that may merit a bit more consideration as a discussion point, when broadly considering the expansion of these various types of interventions. - The authors should briefly highlight some of the limitations of this study.
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REVIEWER	Nasa, Prashant
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	NMC Healthcare LLC, Critical Care Medicine
REVIEW RETURNED	25-Jan-2022

GENERAL COMMENTS	<p>Thank you for this interesting study.</p> <p>Regarding methods of the study, following concerns need to be addressed.</p> <ol style="list-style-type: none"> 1. The first round of Delphi is an open round with involvement of panel members in formulation of the questionnaire. It seems the studies were preselected by steering group using a systematic review. This is a modified Delphi (DOI: 10.5662/wjm.v11.i4.116) 2. Criteria of consensus should be decided a priori. However, criteria of consensus not clear in the methods. 3. 28% and 38% drop-out in round one and two, respectively needs explanation and should be acknowledged in the limitations of the study. 4. Methods in this Delphi are not as per the reference used for Delphi (Dalkey NC et al 1968).
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Maureen Lyon, George Washington University School of Medicine and Health Sciences,
Children's National Hospital

Comments to the Author:

This manuscript is a systematic review and Delphi analysis of intervention studies conducted in South Africa with adolescents (ages 10-24), entitled "Interventions addressing the adolescent HIV continuum of care in South Africa: a systematic review and Delphi analysis" (MS # bmjopen-2021-057797).

This is a very important study which used scientifically rigorous methods to conduct a review of the literature on interventions addressing the HIV continuum. Given HIV/AIDS is the leading cause of death for adolescents in South Africa, the importance of this article for improving the continuum of care for HIV positive adolescents cannot be overstated. The results from this review have the potential for a very high impact on linkages with care of newly diagnosed HIV positive persons, as well as promising approaches that may help transition adolescents to adult health care facilities based on what has worked with engagement in care interventions.

The title appropriately reflects the content of the manuscript.

The abstract is a good summary of the findings and includes all essential elements.

Introduction. The introduction notes the gaps in knowledge particularly with respect to linking newly diagnosed adolescents with care and transitioning HIV positive adolescents to adult health care facilities. The introduction sets up the purpose of the study highlighting what is known. Particularly striking is that only 10% of adolescents living with HIV are virally suppressed, despite one of the largest antiretroviral therapy programs in the world.

Methods.

Use of the PRISMA guidelines is a strength of this study. The Delphi analysis with experts from the National Institutes of Health's Fogarty International Adolescent HIV Implementation Science Alliance—South Africa further strengths the analysis of the findings of this review. A response rate of 50% or more in a survey is considered excellent. The investigators had a response rate of 69% to the

REDCap survey to evaluate the identified studies meeting the inclusion criteria, further strengthening the validity and reliability of the study findings.

Data analysis. Appropriate methods were used for ranking the eligible articles using the PRISMA 2020 Checklist methods, including the experts in the Delphi analysis.

Findings. The findings are clearly presented in the tables and reflected in the text of the manuscript.

The descriptive Tables 1-3 are very clear.

Discussion and conclusion follow from the systematic review. The identify important elements of effective interventions for adolescents that can guide future research into linkages to care and transition to adult health care, as well as what interventions work best, specifically in-home and HIV-self testing, community-based adherence support, and provision of adolescent-friendly services. The authors suggest future research should assess the cost of interventions but given limited resources perhaps the priority should be finding what works most effectively to link adolescents with care, adhere to ART treatment, and to help them transition to adult health care, irrespective of the relative costs, given this is the leading cause of death in South Africa for this age group.

To summarize, identified scalable interventions that could improve the adolescent HIV continuum of care in South Africa that can be acted upon immediately. Investigators also identified gaps in the identification of evidence-based interventions that could effectively link adolescents living with HIV to care and to help the transition to adult health care services.

Investigators report the limitations of their findings in detail and the list is comprehensive.

Response: We thank the reviewer for their thorough review and positive feedback.

1. Page 7 Line 18 "...and scale..." Please consider using the word "scalability" here to parallel the use of the word "feasibility" in the previous phrase.

Response: We have made the correction: Lines 91 – 93:

"The REDCap questionnaire was updated and emailed to AHI(SA)2 members who participated in the first-round questionnaire (n=29) to evaluate feasibility and scalability (September 25, 2020 to December 15, 2020)."

2. Page 9 Line 14 "...nine discussed costing of the intervention." The use of the word "costing" here is awkward. Please consider rewriting.

Response: We have reworded the sentence. Line 123 – 124:

"Two studies of the nine discussed the cost of the intervention."

3. Page 15 Lines 17-20. Although there was no statistically significant difference in community-based support in one study with respect to viral failure after 3-5 years, that 8.8% in the intervention group had viral failure compared to 37.2% in the standard of care group is clinically meaningful and this should be noted. The authors might also want to comment on why this was not statistically significant, e.g. were there so many cases lost to follow up that the sample was too small to find a statistical difference?

Response: We thank the reviewer for highlighting this important point. We have now clarified in the manuscript: Lines 198 – 202:

"Cumulative loss to follow up was lower in the intervention group (30%) compared to standard of care (39%; aHR = 0.60; 95% CI 0.51 – 0.71; p <0.0001). Although there was no statistically significant difference in viral failure after three or five years; 8.8% in the intervention group had viral failure compared to 37.2% in the standard of care group (aOR 0.24, 95%CI 0.06 – 1.03), the difference may be clinically meaningful."

Reviewer: 2

Dr. Maj Casale, Oxford Brookes University Faculty of Health and Life Sciences

Comments to the Author:

This is an overall well-written and well-structured paper on an important topic, given the persistent high loss to follow up across the continuum of care among adolescents and limited evidence of effective interventions – as highlighted by the authors. I also found the combination of a systematic review and Delphi survey original and interesting. I have mainly minor comments for consideration by the authors:

Response: We thank the reviewer for their positive feedback.

1. pg 4: I'm not sure one can refer to expanding implementation of interventions as an objective of the study reported in this paper. Perhaps something along the lines of the identification of promising interventions to be scaled up?

Response: We have clarified the objective to include identification and scale of promising interventions. Lines 25 - 27:

"Our objective was to utilize a network of researchers working to improve HIV care for ALWH in South Africa to identify promising interventions for wider implementation and future scale up of successful interventions for this population."

2. Pgs 4/5: It would be useful to be clearer upfront about the inclusion (versus simply exclusion) criteria for the systematic review, e.g. that the review could include intervention studies aimed at increasing or promoting one of more of the following: testing, linkage to care, retention etc

Response: We have clarified the inclusion criteria. Lines 52 – 55:

"We included randomized controlled trials, pre-post evaluations, and retrospective cohorts that evaluated interventions with primary outcomes addressing the adolescent HIV continuum of care in South Africa."

3. It would be useful to include further information on the search strategy in supplementary material, including an example search string used. It would also be useful to indicate which data were extracted from the papers and presented to Delphi survey participants.

Response: As noted in our comments to the Editor above, we have now included the search strategy as a supplement. We have also included details about the data extracted from the literature. The Delphi participants were given access to the full articles and summary information included in Table 2.

Data extraction: Lines 57 – 59:

"We then extracted data including study population, location, design, intervention description, and outcomes from the full text articles and created summarized tables organized by each step in the HIV continuum of care."

Participants data access: Lines 74 – 76:

"We uploaded summarized tables from our systematic review, along with links to the full text articles and abstracts, into REDCap for participants to access."

4. Similarly, it would be useful to specify in the paper which tool or template was used for assessment of bias/strength of evidence. Perhaps the grading or scoring table could also be included among supplementary material?

Response: Participants were given information based on the GRADE guidelines (for each article, not as a table). We have included this point in the manuscript. Lines 64 -66:

"Observational studies were evaluated for bias using the GRADE guidelines and each article included an assessment of eligibility, controls, loss to follow-up, and outcome consistency (14)."

5. Was there any basis for the cutoff scores used for inclusion of interventions in the second round questionnaire (e.g. impact score above 70)?

Response: The cutoff of 70 was decided a priori by the AHISA leadership as the threshold for studies that would be likely to be scaled. We have added this to the manuscript. Lines 80 – 82:

“AHI(SA)2 leadership decided a priori that a score of 70 or greater would be a reasonable estimate of clinically meaningful effects and would be required to be included in the second-round analysis.”

6. Besides making the case for the potential scale up of specific types of interventions that appear to be both effective and feasible, I wondered whether the authors could extend these arguments to consider the potential for combination or integrated interventions. Do the authors have any thoughts, based on these findings, on the potential to roll out or scale up some of these interventions in combination and how best to do this?

Response: We agree that this is an important point for future intervention studies. We have included in the discussion. Lines 260 – 262:

“Future interventions addressing the adolescent HIV continuum of care should build on the promising results from the highlighted studies and perhaps include a combination of the most effective strategies to optimize outcomes.”

7. Another important point to consider, beyond intervention effectiveness and feasibility, is what adolescents are likely to find acceptable. Work I was recently involved in highlighted concerns around stigma and confidentiality, for example, among potential barriers to adolescent acceptability of interventions

(<https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fbmjopen.bmj.com%2Fcontent%2F11%2F12%2Ffe055160&data=04%7C01%7Cbrian.christopher.zanoni%40emory.edu%7Cead183bb50294f7eed1208d9e04a410e%7Ce004fb9cb0a4424fbc0322606d5df38%7C0%7C0%7C637787431949813757%7CUnknown%7CTWFPbGZsb3d8eyJWljoic4wLjAwMDAiLCJQIjoiV2luMzliLCJBTiI6Ik1haWwiLCJXVCi6Mn0%3D%7C3000&sdata=DG3HCKEnEcpTbsiTCJ7ZYiGMJDJbxcCkmmqisR4%2Fm4%3D&reserved=0>). The authors allude to acceptability briefly in relation to self-testing on page 15 but it is an issue that may merit a bit more consideration as a discussion point, when broadly considering the expansion of these various types of interventions.

Response: We agree that acceptability of the interventions by adolescents is critical to successful intervention design and implementation. We have included in the discussion lines XXX:

“Additionally, acceptability of the interventions by adolescents is critical for continued success of potential interventions. (34) Using participant-centered design and direct input from adolescent early in intervention development can likely increase acceptability and improve likelihood of intervention success (35).”

8. The authors should briefly highlight some of the limitations of this study.

Response: We have highlighted and expanded on some of the limitation of the study. Lines XXX

“This systematic review and modified Delphi analysis has several limitations. First, we only identified interventions that were published in the literature and did not include studies that were in progress or planned. In addition, the modified Delphi analysis did not include researchers who were not yet published, received non-NIH funding, or did not respond to email invitations. However, the AHI(SA)2 network includes highly experienced experts with key knowledge to evaluate interventions in South Africa. In addition, not all AHI(SA)2 members who were invited to participate completed the survey. We experienced drop-out rates of 28% and 38% in rounds one and two of the modified Delphi analysis due to strict completion deadlines prior to scheduled AHI(SA)2 meetings. However, this review highlights published interventions with quantifiable results addressing the continuum of care for adolescents and young adults evaluated by scholars with interest in this population.”

Reviewer: 3

Dr. Prashant Nasa, NMC Healthcare LLC

Comments to the Author:

Thank you for this interesting study.

Regarding methods of the study, following concerns need to be addressed.

1. The first round of Delphi is an open round with involvement of panel members in formulation of the questionnaire. It seems the studies were preselected by steering group using a systematic review.

This is a modified Delphi (DOI: 10.5662/wjm.v11.i4.116)

Response: We have clarified throughout that this is a modified Delphi analysis and have included the suggested reference.

2. Criteria of consensus should be decided a priori. However, criteria of consensus not clear in the methods.

Response: We clarified the a priori criteria of consensus in the methodology. Lines XXX

“AHI(SA)2 leadership decided a priori that a score of 70 or greater would be a reasonable estimate of clinically meaningful effects and would be required to be included in the second-round analysis.”

3. 28% and 38% drop-out in round one and two, respectively needs explanation and should be acknowledged in the limitations of the study.

Response: We have clarified the drop-out rates in the limitations and acknowledge that the strict completion deadlines prior to each AHI(SA)2 meeting contributed to the dropout rates. Lines XXX
“We experienced drop-out rates of 28% and 38% in rounds one and two respectively of the modified Delphi analysis due to strict completion deadlines prior to scheduled AHI(SA)2 meetings.”

4. Methods in this Delphi are not as per the reference used for Delphi (Dalkey NC et al 1968).

Response: The Dalkey reference has been moved and the references updated. See references 16. Nasa, et al. and 17. Jandhyala, et al.

VERSION 2 – REVIEW

REVIEWER	Casale, Maj University of Oxford Department of Social Policy and Intervention
REVIEW RETURNED	01-Mar-2022
GENERAL COMMENTS	I am satisfied with the response to reviewer comments and changes made.
REVIEWER	Nasa, Prashant NMC Healthcare LLC, Critical Care Medicine
REVIEW RETURNED	25-Feb-2022
GENERAL COMMENTS	Thank you for your point-by-point response to all the observations. I am satisfied with the responses. There are no further comments.